Myelodysplastic Syndromes and Other Precursor Myeloid Neoplasms in the Era of Genomic Medicine (Mini Review)

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Abstract

Myeloid neoplasms are derived from precursor cells of myeloid lineage and are composed of a broad spectrum of hematopoietic malignancies. The nature of the myeloid precursor is largely under-investigated until the recent application of next generation sequencing (NGS) technology for genome-wide analysis of myeloid neoplasms. It is important to define precursor myeloid neoplasms mediated by molecular signatures including driver gene mutations essential in disease initiation as well as acquired genetic alterations that play a role in disease progression.

In addition to myelodysplastic syndromes with a high risk of leukemic transformation, there are newly proposed early precursor disorders with the potential to evolve into myeloid neoplasms [e.g., clonal hematopoiesis of indeterminate potential (CHIP), and clonal cytopenias of undetermined significance (CCUS)]. Furthermore, certain predisposing germline mutations (e.g. CEBPA, DDX41, RUNX1, ETV6 and GATA) have been recognized with predisposition to develop into myeloid neoplasms.

This review paper aims to provide a brief summary of novel concepts of early precursor lesions that could lead to myeloid neoplasms, potential molecular prognostic indicators for MDS, and updated sub-classification of myelodysplastic syndromes according to the 2016 revision of World Health Organization (WHO).

Mini Review

Myelodysplastic syndromes (MDS) are considered one of the major precursor myeloid neoplasms. It is defined as a group of clonal hematopoietic stem cell neoplasms characterized by bone marrow failure with manifestations of peripheral cytopenia, morphologic dysplasia involving ≥ 1 hematopoietic lineages, variably increased blasts (<20%), and an increased risk of leukemic transformation [1,2]. Given its heterogeneous clinical and histologic presentation and the various morphologic mimickers in reactive or autoimmune situations, it is a diagnostic challenge if no clonal cytogenetic abnormalities are found [3,4]. Moreover, it is sometimes difficult evaluating the degree of morphologic dysplasia or cytopenia.

The 2008 World Health Organization (WHO) classification integrated laboratory data, morphology, and cytogenetic findings to subclassify MDS. The updated 2016 revision of the WHO has modified the subclassification of MDS based on novel molecular data (Table 1) [5,6].

In light of the new criteria in acute myeloid leukemia (AML), the 2016 revision of the WHO will also include a subset of patients who were previously diagnosed “erythroleukemia -erythroid/myeloid” with the absolute myeloblast count <20% of the total cellularity, regardless the percentage of erythroid precursors [5]. The comparison of the terms used in subclassification of MDS in 2008 and 2016 WHO system are shown in Table 1 [1,5].

Cytogenetic studies including conventional karyotyping and fluorescence in situ hybridization (FISH) are common ancillary diagnostic tools. Of note, approximately 50% of de novo MDS and 75% of secondary or therapy-related MDS harbor cytogenetic aberrations, frequently associated with del(7q), monosomy 7, del(5q), monosomy 5, and trisomy 8.

Among them, MDS with isolated del(5q) is considered a unique, independent subtype with characteristic megakaryocytic anomaly, macrocytic anemia and erythroid hypoplasia; however, there is no cytogenetic abnormality specific for MDS.

Nevertheless, these cytogenetic changes are taken into account in international prognostic scoring system (IPSS) and revised IPSS (R-IPSS) in predicting patient outcome (Table 2a and 2b) [7,8]. IPSS and R-IPSS have been widely accepted in clinical practice for the last decade until a recent multicenter study established a new prognostic system.

Data collected from 7,212 patients with untreated de novo MDS demonstrated the risk of transformation and mortality changed over time. Hazard scores regarding morality and transformation to AML were reduced in high-risk MDS while remaining stable in low-risk MDS when analyzed at 3.5 years from initial diagnosis [9].

The results led to the proposal of using the new cut-off of 3.5 points in R-IPSS to separate low from high-risk groups for the purpose of treatment management.

The other risk-stratification systems, such as the WHO classification–based prognostic scoring system (WPSS) and MD Anderson MDS scoring system have been validated and adopted as needed [10-13].
Emerging next generation sequencing (NGS) technique makes it feasible to identify recurrent somatic mutations in cancer cells and also highlights frequency and importance of these somatic mutations in MDS. Up to 80-90% of MDS patients harbor one or more recurring mutations including AXSL1, ETV6, TP53, RUNX1 and EZH2 showed short median overall survival when compared with the MDS patients with unilineage or multilineage dysplasia (MDS-SLD). TP53 mutations is associated with shorter overall survival [14].

Prognostic importance, patients harboring five key gene mutations including AXSL1, ETv6, TP53, RUNX1 and EZH2 showed short median overall survival when compared with the MDS patients in the same risk group (very low risk, low risk, and intermediate risk) according to R-IPSS [14].

Table 1: Comparison of the terms used in subclassification of MDS in 2008 and 2016 WHO System and classifications no longer used in the 2016 revision of the WHO classification.

2008 WHO classification | 2016 Revision of WHO classification
--- | ---
Refractory cytopenia with unilineage dysplasia | MDS with single lineage dysplasia (MDS-SLD)
Refractory anemia (RA) | -
Refractory neutropenia (RN)* | -
Refractory thrombocytopenia (RT)* | -
Refractory anemia with ring sideroblasts (RARS) | MDS with ring sideroblasts (MDS-RS)
- | MDS with RS and single lineage dysplasia (MDS-RS-SLD)
- | MDS with RS and multilineage dysplasia (MDS-RS-MLD)
Refractory cytopenia with multilineage dysplasia (RCMD) | MDS with multilineage dysplasia (MDS-MLD)
Refractory anemia with excess blasts (RAEB) | MDS with excess blasts (MDS-EB)
Refractory anemia with excess blasts, type I (RAEB-I) | MDS with excess blasts, type I (MDS-EB-I)
Refractory anemia with excess blasts, type II (RAEB-II) | MDS with excess blasts, type II (MDS-EB-II)
MDS, with isolated del (5q) | MDS with isolated del(5q)
MDS, unclassifiable | MDS, unclassifiable
Provisional entity: Childhood MDS: refractory cytopenia of childhood (RCC) | Provisional entity: Refractory cytopenia of childhood (RCC)

Table 2a: Prognostic score values in IPSS and R-IPSS.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic classification</td>
<td>Very good</td>
</tr>
<tr>
<td>Blast count (% in BM)</td>
<td>≤2%</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>≥10</td>
</tr>
<tr>
<td>Platelets (k/uL)</td>
<td>≥100</td>
</tr>
<tr>
<td>ANC (k/uL)</td>
<td>≥0.8</td>
</tr>
</tbody>
</table>

*Definition of cytogenetics in IPSS: good = normal, -Y, del(5q), del(20q); poor = complex (≥3 abnormalities) or chromosome 7 anomalies; intermediate = other abnormalities
**Definition of cytogenetics in R-IPSS: good = -Y, del(11q); good = normal, del(5q), del(12p), del(20q), double including del(5q); intermediate = del(9q), +8, +19, i(17q), any other single or double independent clones; poor = -7, inv(3)/t(3q), double including -7; del(7q); complex: 3 abnormalities; very poor: complex: >3 abnormalities.

Addition data might be helpful in integrating it into daily practice

IPSS

Table 2b: Prognostic score values in IPSS and R-IPSS.

<table>
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Addition data might be helpful in integrating it into daily practice
mutations, 2) myeloid neoplasms with germline RUNX-1, ANKR26 or ETV6 mutations which often have preexisting platelet disorder, and 3) myeloid neoplasms with germline mutations accompanying organ dysfunction (e.g., Down syndrome, neurofibromatosis, Noonien syndrome, telomere disorder or GATA2 mutation) [5]. An accurate diagnosis of MNGP requires a thorough family history looking for symptoms of MDS and genetic investigation. There is no discrete treatment plan for the aforementioned situations. However, the increased potential for development of myeloid neoplasm (e.g., MDS or AML) in patients with familial genetic alterations or mutations warrants close clinical monitoring and follow-up.

Table 2b: Risk group and clinical outcome in IPSS and R-IPSS.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Score</th>
<th>Risk of leukemic transformation (years)</th>
<th>Overall survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>9.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Intermediate I</td>
<td>0.5-1.0</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Intermediate II</td>
<td>1.5-2.0</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt;2.0</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>R-IPSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
<td>NR</td>
<td>9.3</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3</td>
<td>NR</td>
<td>6.3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3-4.5</td>
<td>2.4</td>
<td>3.4</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5-6</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
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Table 2b: Risk group and clinical outcome in IPSS and R-IPSS.

Conclusion

In summary, in the era of molecular diagnosis and personalized medicine, it is important to pay attention to precursor lesions (e.g. CHIP, ICUS, CCUS and MNGP) that could lead to MDS or AML. Integrating morphology, immunophenotype, genetic profile, new WHO subclassification, and risk stratification according to IPSS and R-IPSS is necessary for accurate diagnosis and appropriate management in MDS patients.

References